

## SEQUENCE LISTING

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<120> Method For Accelerating The Rate of Mucociliary Clearance

<130> 98-736-A

<140> US 09/441,966

<141> 1999-11-17

<150> US 09/218,913

<151> 1998-12-22

<160> 105

<170> PatentIn version 3.1

<210> 1

<211> 179

<212> PRT

<213> Homo sapiens

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Asn Asn Tyr Leu Thr Lys Glu Glu Cys Leu Lys Lys Cys Ala Thr Val 50 55 60

Thr Glu Asn Ala Thr Gly Asp Leu Ala Thr Ser Arg Asn Ala Ala Asp 65 70 75 80

Ser Ser Val Pro Ser Ala Pro Arg Arg Gln Asp Ser Glu Asp His Ser 85 90 95

Ser Asp Met Phe Asn Tyr Glu Glu Tyr Cys Thr Ala Asn Ala Val Thr
100 105 110

Gly Pro Cys Arg Ala Ser Phe Pro Arg Trp Tyr Phe Asp Val Glu Arg

for

 $M^{5}$ 

115 120 125

Asn Ser Cys Asn Asn Phe Ile Tyr Gly Gly Cys Arg Gly Asn Lys Asn 130 135 140

Ser Tyr Arg Ser Glu Glu Ala Cys Met Leu Arg Cys Phe Arg Gln Gln 145 155 160

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Lys Val Val Gly Arg Cys Arg Ala Ser Met Pro Arg Trp Trp Tyr Asn 35 40 45

Val Thr Asp Gly Ser Cys Gln Leu Phe Val Tyr Gly Gly Cys Asp Gly 50 55 60

Asn Ser Asn Asn Tyr Leu Thr Lys Glu Glu Cys Leu Lys Lys Cys Ala 65 70 75 80

Thr Val Thr Glu Asn Ala Thr Gly Asp Leu Ala $\sqrt{}$ Thr Ser Arg Asn Ala 85 90 95

Ala Asp Ser Ser Val Pro Ser Ala Pro Arg Arg Gla Asp Ser Glu Asp

His Ser Ser Asp Met Phe Asn Tyr Glu Glu Tyr Cys Thr Ala Asn Ala 115 120 125

Val Thr Gly Pro Cys Arg Ala Ser Phe Pro Arg Trp Tyr Phe Asp Val

Glu Arg Asn Ser Cys Asn Asn Phe Ile Tyr Gly Gly Cys Arg Gly Asn 145 150 155 160

Lys Asn Ser Tyr Arg Ser Glu Glu Ala Cys Met Leu Arg Cys Phe Arg 165 170 175

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Phe Val Tyr Gly Gly Cys Asp Gly Asn Ser Asn Asn Tyr Leu Thr Lys 35 40 45

Glu Glu Cys Leu Lys Lys Cys Ala Thr Val Thr Glu Asn Ala Thr Gly
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Asp Leu Ala Thr Ser Arg Asn Ala Ala Asp Ser Ser Val Pro Ser Ala 65 70 75 80

Pro Arg Arg Gln Asp Ser Glu Asp His Ser Ser Asp Met Phe Asn Tyr 85 90 95

as Cont

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Glu Glu Tyr Cys Thr Ala Asn Ala Val Thr Gly Pro Cys Arg Ala Ser
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Phe Pro Arg Trp Tyr Phe Asp Val Glu Arg Asn Ser Cys Asn Asn Phe
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Glu Glu Cys Leu Lys Lys Cys Ala Thr Val
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Glu Ala Cys Met Leu Arg Cys Phe Arg Gln
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Trp Tyr Phe Asp Val Glu Arg Asn $er Cys Asn Asn Phe Ile Tyr Gly
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Asn Asn Tyr Leu Thr Lys Glu Glu Cys Leu Lys Lys Cys Ala Thr Val
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abla \operatorname{\mathsf{tcctc}} tctggggtcc \operatorname{\mathsf{tggcggccga}}
                                                                                 60
ccgagaacgc agcatccacg acttctgcct ggtgtdgaag gtggtgggca gatgccgggc
                                                                                120
ctccatgcct aggtggtggt acaatgtcac tgacggdtcc tgccagctgt ttgtgtatgg
                                                                                180
gggctgtgac ggaaacagca ataattacct gaccaaggag gagtgcctca agaaatgtgc
                                                                                240
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cactgtcaca gagaatgcca cgggtgacct ggccaccagc aggaatgcag cggattcctc

	•					
tgtcccaagt	gctcccagaa	ggcaggattc	tgaagaccac	tccagcgata	tgttcaacta	360
tgaagaatac	tgcaccgcca	acgcagtcac	tgggccttgc	cgtgcatcct	tcccacgctg	420
gtactttgac	gtggagagga	actcctgcaa	taacttcatc	tatggaggct	gccggggcaa	480
taagaacagc	taccgctctg	aggaggcctg	catgctccgc	tgcttccgcc	agcaggagaa	540
tcctcccctg	ccccttggdt	caaaggtggt	ggttctggcc	ggggctgttt	cgtgatggtg	600
ttgatccttt	tcctggggag	catccatggt	cttactgatt	ccgggtggca	aggaggaacc	660
aggagcgtgc	cctgcgganc	gtctggagct	tcggagatga	caagggnt		708
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<223> Amino acids -18 to 179 of translation of consensus sequence in Fig. 3.

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Leu Ala Ala Asp Arg Glu Ard Ser Ile His Asp Phe Cys Leu Val Ser 20 25 30

Lys Val Val Gly Arg Cys Arg Ala Ser Met Pro Arg Trp Trp Tyr Asn 35 40 45

Val Thr Asp Gly Ser Cys Gln Leu Phe Val Tyr Gly Gly Cys Asp Gly 50 55 60

Asn Ser Asn Asn Tyr Leu Thr Lys Glu Glu Cys Leu Lys Lys Cys Ala
65 70 75 80

Thr Val Thr Glu Asn Ala Thr Gly Asp Leu Ala Thr Ser Arg Asn Ala 85 90 95

Ala Asp Ser Ser Val Pro Ser Ala Pro Arg Arg Gln Asp Ser Glu Asp
100 105 110

His Ser Ser Asp Met Phe Asn Tyr Glu $\sqrt{\text{Glu Tyr Cys Thr Ala Asn Ala}}$  125

pur Bl

as Cont

Val Thr Gly Pro Cys Arg Ala Ser Phe Pro Arg Trp Tyr Phe Asp Val 130 135 Glu Arg Asn Ser Cys As $\mathfrak h$  Asn Phe Ile Tyr Gly Gly Cys Arg Gly Asn 145 Lys Asn Ser Tyr Arg Ser\Glu Glu Ala Cys Met Leu Arg Cys Phe Arg 165 170 Gln Gln Glu Asn Pro Pro Leu Pro Leu Gly Ser Lys Val Val Leu 185 Ala Gly Ala Val Ser 195 <210> 11 <211> 179 <212> PRT <213> Artificial Sequence <220> <223> Variants of human Bikunin. <220> <221> MISC\_FEATURE <222> (8)..(8) Each "Xaa" independently represents a naturally occurring amino acid residue except Cys, with the proviso that at least one "Xaa" <223> in SEQ ID NO:11 is different from the corresponding amino acid residue of the native sequence (see page 10 of specification). <220> <221> MISC\_FEATURE <222> (17)..(17)<223> Each "Xaa" independently represents a naturally occurring amino acid residue except Cys, with the proviso that at least one "Xaa" in SEQ ID NO:11 is different from the corresponding amino acid residue of the native sequence (see page 10 of specification). <220> <221> MISC\_FEATURE <222> (19)..(19) <223> Each "Xaa" independently represents a naturally occurring amino acid residue except Cys, with the proviso that at least one "Xaa" in SEQ ID NO:11 is different from the corresponding amino acid residue of the native sequence (see page 10 of specification). <220> <221> MISC\_FEATURE

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Each "Xaa" independently represents a naturally occurring amino acid residue \except Cys, with the proviso that at least one "Xaa" in SEQ ID NO: 11 is different from the corresponding amino acid residue of the native sequence (see page 10 of specification).

<220>

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Each "Xaa" independently represents a naturally occurring amino <223> acid residue except Cys, with the proviso that at least one "Xaa" in SEQ ID NO:11 is different from the corresponding amino acid residue of the native sequence (see page 10 of specification).

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<220> <221> MISC\_FEATURE <222> (112)..(112)Each "Xaa" independently represents a naturally occurring amino <223> acid residue except Cys, with the proviso that at least one "Xaa" in SEQ ID NO:14 is different from the corresponding amino acid residue of the native sequence (see page 10 of specification). <220> <221> MISC\_FEATURE <222> (114)..(114)<223> Each "Xaa" independently represents a naturally occurring amino acid residue except Cys, with the proviso that at least one "Xaa" in SEQ ID NO:11 is different from the corresponding amino acid residue of the native sequence (see page 10 of specification). <220> <221> MISC\_FEATURE <222> (116)..(121) <223> Each "Xaa" independently represents a naturally occurring amino acid residue except Cys, with the proviso that at least one "Xaa" in SEQ ID NO:11 is different from the corresponding amino acid residue of the native sequence (see page 10 of specification). <220> <221> MISC\_FEATURE <222> (135)..(135)<223> Each "Xaa" independently represents a naturally occurring amino acid residue except Cys, with the proviso that at least one "Xaa" in SEQ ID NO:11 is different from the corresponding amino acid residue of the native sequence (see page 10 of specification). <220> <221> MISC\_FEATURE <222> (137)..(137)<223> Each "Xaa" independently represents a naturally occurring amino acid residue except Cys, with the proviso that at least one "Xaa" in SEQ ID NO:11 is different from the corresponding amino acid residue of the native sequence (see page 10 of specification). <220>

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(140)..(142)

acid residue except Cys, with the proviso that at least one "Xaa" in SEQ ID NO:11 is different from the corresponding amino acid residue of the native sequence (see page 10 of specification).

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       residue of the native sequence (see page 10 of specification).
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Ala Asp Arg Glu Arg Ser Il& Xaa Asp Phe Cys Leu Val Ser Lys Val
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                                 25
Asp Gly Ser Cys Gln Leu Phe Xaa Tyr Xaa Gly Cys Xaa Xaa Xaa Ser
        35
Asn Asn Tyr Xaa Thr Lys Glu Glu Cys Leu Lys Lys Cys Ala Thr Xaa
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                         55
                                             60
Thr Glu Asn Ala Thr Gly Asp Leu Ser Thr Ser Arg Asn Ala Ala Asp
65
                     70
                                         75
                                                              80
Ser Ser Val Pro Ser Ala Pro Arg Atg Gln Asp Ser Glu His Asp Ser
Ser Asp Met Phe Asn Tyr Xaa Glu Tyt Cys Thr Ala Asn Ala Val Xaa
            100
                                 105
                                                      110
Gly Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa Trp Tyr Phe Asp Val Glu Arg
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                             120
                                                  125
Asn Ser Cys Asn Asn Phe Xaa Tyr Xaa Gl∜ Cys Xaa Xaa Xaa Lys Asn
    130
                         135
                                             140
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Ser Tyr Xaa Ser Glu\Glu Ala Cys Met Leu Arg Cys Phe Arg Xaa Gln
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                                                                       120
cctccatgcc taggtggtgg tacaatgtca ctgacggat
abla ctgccagctg tttgtgtatg
                                                                       180
ggggctgtga cggaaacagc aataattacc tgaccaagga/ggagtgcctc aagaaatgtg
                                                                       240
ccactgtcac agagaatgcc acgggtgacc tggccaccag caggaatgca gcggattcct
                                                                       300
ctgtcccaag tgctcccaga aggcaggatt cttgaagacc &cttcagcga tatgtttcaa
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Lys Val Val Gly Arg Glu Arg Ala Ser Met Pro Arg Trp Trp Tyr Asn
        35
Val Thr Asp Gly Ser Cys Gln Leu\Phe Val Tyr Gly Gly Cys Asp Gly
    50 ·
                        55
Asn Ser Asn Asn Tyr Leu Thr Lys dlu Glu Cys Leu Lys Lys Cys Ala
65
                    70
                                        75
                                                             80
Thr Val Thr Glu Asn Ala Thr Gly Ash Leu Ala Thr Ser Arg Asn Ala
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Ala Asp Ser Ser Val Pro Ser Ala Pro Arg Arg Gln Asp Ser
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                                                                      120
aaggcaggat totgaagaco a¢tocagoga tatgttcaac tatgaagaat actgcacogo
                                                                      180
caacgcagtc actgggcctt gckgtgcatc cttcccacgc tggtactttg acgtggagag
                                                                      240
gaactcctgc aataacttca tctatggagg ctgccggggc aataagaaca gctaccgctc
                                                                      300
tgaggaggcc tgcatgctcc gctgcttccg ccagcaggag aatcctcccc tgccccttgg
                                                                      360
ctcaaaggtg gtggttctgg ccggggctgt ttcgtgatgg tgttgatcct tttcctgggg
                                                                      420
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agaacgcagc atccacgact tctgcctggt gtcgaaggtg gtgggcagat gccgggcctc
                                                                      120
catgcctagg tggtggtaca atgccactga cggatcctgc cagctgtttg tgtatggggg
                                                                      180
ctgtgacgga aacagcaata attacctgac caaggaggag tgcctcaaga aatgtgccac
                                                                      240
tgtcacagag aatgccacgg gtgacctggc caccagcagg aatgcagcgg attcctctgt
                                                                      300
cccaagtgct cccagaaggc agdattctga agaccactcc agcgatatgt tcaactatga
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agaatactgg caccgccaac gcattcactg ggcctgcgtg catccttccc acgctggtac
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                                                                       120
aatgtcactg acggatcktg ccagctgttt gtgtatgggg gctgtgacgg aaacagcaat
                                                                       180
aattacctga ccaaggadga gtgcctcaag aaatgtgcca ctgtcacaga gaatgccacg
                                                                       240
ggtgacctgg ccaccagcag gaatgcagcg gattcctctg tcccaagtgc tcccagaagg
                                                                       300
caggattetg aagaccacte cagegatatg tteaactatg aagaatactg caeegeeaac
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gcagtcactg ggccttgcgt ggaatccttt cccacgctgg naatttngac gttgagaagg
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aac
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Met Lys Arg Phe Phe Phe Asn Ile Phe Thr Arg Gln Cys Glu Glu Phe
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Ile Tyr Gly Gly Cys Glu Gly Asn Gln Asn Arg Phe Glu Ser Leu Glu
                             40
Glu Cys Lys Lys Met Cys Thit Arg Asp
    50
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Pro Asp Phe Cys Phe Leu Glu Glu Asp Pro Gly Ile Cys Arg Gly Tyr
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Ile Thr Arg Tyr Phe Tyr Asn Asn Gln Thr Lys Gln Cys Glu Arg Phe
            20
Lys Tyr Gly Gly Cys\Leu Gly Asn Met Asn Asn Phe Glu Thr Leu Glu
        35
                            40
Glu Cys Lys Asn Ile Cys Glu Asp Gly
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Pro Ser Trp Cys Leu Thr Pro Ala Asp Arg Gly Leu Cys Arg Ala Asn
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                                    10
Glu Asn Arg Phe Tyr Tyr Asn Ser Val Ile Gly Lys Cys Arg Pro Phe
            20
Lys Tyr Ser Gly Cys Gly Gly Asn Glu Asn Asn Phe Thr Ser Lys Gln
Glu Cys Leu Arg Ala Cys Ly$ Lys Gly
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<223> Kunitz-like domain of tissue factor pathway inhibitor precursor 2.
<400> 21
Ala Glu Ile Cys Leu Leu Pro Leu Asp Tyr Gly Pro Cys Arg Ala Leu
                5
                                    10
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Leu Tyr Gly Gly Cy Glu Gly Asn Ala Asn Asn Phe Tyr Thr Trp Glu
                            40
Ala Cys Asp Asp Ala Cys Trp Arg Ile
    50
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      Kunitz-like domain of tissue factor pathway inhibitor precursor 2.
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Val Thr Arg Tyr Tyr Phe∖Asn Pro Arg Tyr Arg Thr Cys Asp Ala Phe
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Asp Ser Lys Arg Ala Cys Ala Lys Ala
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Ile Thr Gly Gly Cys Gly Gly Ash Arg Asn Asn Phe Glu Ser Glu Asp
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Phe Val Tyr Gly Gly Cys Arg Ala Lys Arg Asn Asn Phe Lys Ser Ala
Glu Asp Cys Met Arg Thr Cys Gly Gly Ala
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Gly Cys Met Gly Asn Gly Asn Asn Phe Val Thr Glu Lys Glu Cys Leu
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Gln Thr Cys 50

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ab	cgtgcatcct tcccacgctg gtactttgac gtggagagga actcctgcaa taacttcatc	120
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certge	cgtg catcettece achetggtae tttgaegtgg agagg	105
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	Julian Julian grant gag gag coocci coacgecaaa	
gtaccac	rca \	129

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                                                                      180
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Gly Gly Cys Asp Gly Asn Ser Asn Asn Tyr Leu Thr Lys Glu Glu Cys
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Leu Lys Lys Cys Ala Thr Val thr Glu Asn Ala Thr Gly Asp Leu Ala
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Thr Ser Arg Asn Ala Ala Asp Ser Ser Val Pro Ser Ala Pro Arg Arg
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Cys Thr Ala Asn Ala Val Thr Gly Pro Cys Arg Ala Ser Phe Pro Arg
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Trp Tyr Phe Asp Val Glu Arg Asn Ser Cys Asn Asn Phe Ile Tyr Gly
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Gly Cys Arg Gly Asn Lys Asn Ser Tyr Arg Ser Glu Glu Ala Cys Met
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                                     170
                                                         175
Leu Arg Cys Phe Arg Gln Gln Glu Asn Pro Pro Leu Pro Leu Gly Ser
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                                                     190
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60

Met Ala Gln Leu Cy\$ Gly Leu Arg Arg Ser Arg Ala Phe Leu Ala Leu ctg gga tcg ctg ctc/ctc tct ggg gtc ctg gcg gcc gac cga gaa cgc 156 Leu Gly Ser Leu Leu Leu Ser Gly Val Leu Ala Ala Asp Arg Glu Arg age ate cae gae tte toge etg gtg teg aag gtg gtg gge aga tge egg 204 Ser Ile His Asp Phe Cys Leu Val Ser Lys Val Val Gly Arg Cys Arg 40 gcc tcc atg cct agg tdg tgg tac aat gtc act gac gga tcc tgc cag 252 Ala Ser Met Pro Arg Thp Trp Tyr Asn Val Thr Asp Gly Ser Cys Gln ctg ttt gtg tat ggg gg/c tgt gac gga aac agc aat aat tac ctg acc 300 Leu Phe Val Tyr Gly Gly Cys Asp Gly Asn Ser Asn Asn Tyr Leu Thr 70 75 aag gag gag tgc ctc aag aaa tgt gcc act gtc aca gag aat gcc acg 348 Lys Glu Glu Cys Leu Ly\$ Lys Cys Ala Thr Val Thr Glu Asn Ala Thr 90 ggt gac ctg gcc acc ag $\mathfrak{q}$  agg aat gca gcg gat tcc tct gtc cca agt 396 Gly Asp Leu Ala Thr Ser Arg Asn Ala Ala Asp Ser Ser Val Pro Ser 100 105 110 gct ccc aga agg cag gat tct gaa gac cac tcc agc gat atg ttc aac 444 Ala Pro Arg Arg Gln Asp\Ser Glu Asp His Ser Ser Asp Met Phe Asn 115 120 tat gaa gaa tac tgc acc gcc aac gca gtc act ggg cct tgc cgt gca 492 Tyr Glu Glu Tyr Cys Thr Ala Asn Ala Val Thr Gly Pro Cys Arg Ala tee tte eea ege tgg tae tt gae gtg gag agg aac tee tge aat aac 540 Ser Phe Pro Arg Trp Tyr Phe Asp Val Glu Arg Asn Ser Cys Asn Asn 150 155 tto ato tat gga ggc tgc c\u00edg ggc aat aag aac agc tac cgc tot gag 588 Phe Ile Tyr Gly Gly Cys Atg Gly Asn Lys Asn Ser Tyr Arg Ser Glu 165 170 gag gcc tgc atg ctc cgc tgc ttc cgc cag cag gag aat cct ccc ctg 636 Glu Ala Cys Met Leu Arg Cys Phe Arg Gln Gln Glu Asn Pro Pro Leu 180 185 190 ccc ctt ggc tca aag gtg gtg gtt ctg gcg ggg ctg ttc gtg atg gtg 684 Pro Leu Gly Ser Lys Val Val Val Leu Ala Gly Leu Phe Val Met Val 195 200 ttg atc ctc ttc ctg gga gcc|tcc atg gtc tac ctg atc cgg gtg gca 732 Leu Ile Leu Phe Leu Gly Ala Ser Met Val Tyr Leu Ile Arg Val Ala 210 215 cgg agg aac cag gag cgt gcc ctg cgc acc gtc tgg agc ttc gga gat 780 Arg Arg Asn Gln Glu Arg Ala Leu Arg Thr Val Trp Ser Phe Gly Asp

Bubble

as conti

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Pro Leu Gly Ser Lys Val Val Leu Ala Gly Leu Phe Val Met Val
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                            200
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                                                                      120
ccacactgaa ggtccggaaa ggcgacttcc gggggctttg gcacctggcg gaccctcccg
                                                                      180
gagegtegge acetgaaege gaggegetee attgegegtg egegttgagg ggetteeege
                                                                      240
acctgatege gagaceceaa eggetggtgg ¢gtegeetge gegtetegge tgagetggee
                                                                      300
atg gcg cag ctg tgc ggg ctg agg c\psig agc cgg gcg ttt ctc gcc ctg
                                                                      348
Met Ala Gln Leu Cys Gly Leu Arg A‡g Ser Arg Ala Phe Leu Ala Leu
                5
                                    10
ctg gga tcg ctg ctc ctc tct ggg gtc ctg gcg gcc gac cga gaa cgc
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Leu Gly Ser Leu Leu Leu Ser Gly Val Leu Ala Ala Asp Arg Glu Arg
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							gac Asp									540
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							aat Asn									636
							gaa Glu 120									684
							aac Asn						_	_	_	732
							gac Asp									780
							ggc Gly									828
		Cys		Leu			ttc Phe					Asn				876
							gtt Val 200									924
							tcc Ser									972
							ctg Leu									1020
							aac Asn					tgad	cege	cct		1066
gtcg	gccaa	ıga ç	gact	gggg	ga aç	ggag	1999	a gac	ctato	gtgt	gago	ctttt	tt t	aaat	agagg	1126

enog!

as Cont

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aagttttta	ttagcattct	gaadgaagga	aagtaaaatg	tacaagttta	ataaaaaggg	1486
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SIGNAL

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Homo sapiens

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Ser Ile His Asp Phe Cys Leu Val Ser Lys Val Val Gly Arg Cys Arg 35 40 45

Ala Ser Met Pro Arg Trp Trp Tyr Asn Val Thr Asp Gly Ser Cys Gln 55

Leu Phe Val Tyr Gly Gly Cys Asp Gly Asn Ser Asn Asn Tyr Leu Thr 75

Lys Glu Glu Cys Leu Lys Lys Cys Ala Thr Val Thr Glu Asn Ala Thr 85 90 95

Gly Asp Leu Ala Thr Ser Arg Asn Ala Ala Asp Ser Ser Val Pro Ser 105 100

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                                                    190
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Lys Lys Cys Ala Thr Val Thr Glu Asn Ala Thr Gly Asp Leu Ala Thr
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Tyr Phe Asp Val Glu Arg Asn \Ser Cys Asn Asn Phe Ile Tyr Gly Gly
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Asn Asn Tyr Leu Thr Lys Glu Glu Cys Leu Lys Lys Cys Ala Thr Val
50 60

Thr Glu Asn Ala Thr Gly Asp Leu Ala Thr Ser Arg Asn Ala Ala Asp 65 70 75 80

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Ser Asp Met Phe Asn Tyr Glu Glu Tyr Cys Thr Ala Asn Ala Val Thr

Gly Pro Cys Arg Ala Ser Phe Hro Arg Trp Tyr Phe Asp Val Glu Arg 115 120 125

Asn Ser Cys Asn Asn Phe Ile Tyr Gly Gly Cys Arg Gly Asn Lys Asn 130 135 140

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<213>
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Leu Leu Ser Gly Val Leu Ala
           20
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<211> 102
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      5' sense oligonucleotide used for construct #2 in Example 5.
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60
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                                                                 102
<210>
      56
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      129
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<213>
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      3' antisense oligonucle tide used for construct #2 in Example 5.
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actggatcet cattggcgaa aacateteaa catacagget tetteagate tgtaagaatt
                                                                  60
tttattacct ctacaaccac cgtaaataa& attattacaa gaatttcttt caacatcaaa
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gtaccatct
                                                                 129
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      57
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      108
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      5' sense oligonucleotide used for construct #3 in Example 5.
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gaaggggtaa gettggataa aagaaattae gaagaataet gtaetgetaa tgetgttaet
                                                                  60
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ggtccatgta gagcttcttt tccaagatgg tactttgatg ttgaaaga
                                                                      108
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gctgttactg gtccatgtag agcttctttt ccaagatggt actttgatgt tgaaaga
                                                                      117
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       Sense oligonucleptide used in PCR in Example 8.
<400> 59
cacctgatcg cgagacccc
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<210> 60
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      Antisense oligonudleotide used in PCR in Example 8.
<400>
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                                                                      23
ctggcggaag cagcggagca tgc
<210>
       61
<211>
      45
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      Oligonucleotide used in in vitro mutagenesis in Example 9.
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<213> Artificial Sequence
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<212> PRT
<213> Homo sapiens
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<213>
      Homo sapiens
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      64
Ala Asp Arg Glu Arg Ser Ile His Asp Phe Cys Leu Val Ser Lys Val
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                                                        15
Val Gly Arg Cys
            20
<210> 65
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      Homo sapiens
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Phe Asn Tyr Glu Glu Tyr Cys Thr Ala Asn Ala Val Thr Gly Pro Cys
                5
Arg Ala Ser Phe
            20
<210> 66
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<213> Homo sapiens
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Pro Arg Tyr Val Asp Gly Ser Gln Phe Tyr Gly
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<400> 70

Ala Asp Arg Glu Arg Ser Ile His Asp Phe Cys Leu Val Ser Lys Val
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Val Gly Arg Cys Arg Ala Ser Met Pro Arg Trp Trp Tyr Asn Val Thr 20 25 30

Asp Gly Ser Cys Gln Leu Phe Val Tyr Gly Gly Cys Asp Gly Asn Ser 35 40 45

Asn Asn Tyr Leu Thr Lys Glu Glu Cys Leu Lys Lys Cys Ala Thr Val
50 60

Thr Glu Asn Ala Thr Gly Asp Leu Ala Thr Ser Arg Asn Ala Ala Asp 65 70 75 80

Ser Ser Val Pro Ser Ala Pro Arg Arg Gln Asp Ser Glu Asp His Ser 85 90 95

Ser Asp Met Phe Asn Tyr Glu Glu Tyr Cys Thr Ala Asn Ala Val Thr
100 105 110

Gly Pro Cys Arg Ala Ser Phe Pro Arg Trp Tyr Phe Asp Val Glu Arg
115 120 125

Asn Ser Cys Asn Asn Phe Ile Tyr Gly Gly Cys Arg Gly Asn Lys Asn 130 135 140

Ser Tyr Arg Ser Glu Glu Ala Cys Met Leu Arg Cys Phe Arg Gln Gln 145 150 155 160

Ruse Bo

 $\mathcal{U}^{5}$ 

Glu Asn Pro Pro Leu Pr $\phi$  Leu Gly Ser Lys Val Val Leu Ala Gly 165 170 Leu Phe Val Met Val Leu Ile Leu Phe Leu Gly Ala Ser Met Val Tyr 185 Leu Ile Arg Val Ala Arg Arg Asn Gln Glu Arg Ala Leu Arg Thr Val 195 200 205 Trp Ser Phe Gly Asp 210 <210> 71 <211> 225 <212> PRT <213> Homo sapiens <400> 71 Ala Asp Arg Glu Arg Ser Ile His Asp Phe Cys Leu Val Ser Lys Val 5 15 10 Val Gly Arg Cys Arg Ala Set Met Pro Arg Trp Trp Tyr Asn Val Thr Asp Gly Ser Cys Gln Leu Phe Val Tyr Gly Gly Cys Asp Gly Asn Ser 40 Asn Asn Tyr Leu Thr Lys Glu Glu Cys Leu Lys Lys Cys Ala Thr Val 55 Thr Glu Asn Ala Thr Gly Asp Leu Ala Thr Ser Arg Asn Ala Ala Asp 65 70 75 Ser Ser Val Pro Ser Ala Pro Arg Arg Gln Asp Ser Glu Asp His Ser 85 90 95 Ser Asp Met Phe Asn Tyr Glu \$\text{\$\ext{\$\exitit{\$\ext{\$\text{\$\text{\$\text{\$\exitit{\$\text{\$\text{\$\text{\$\exitit{\$\ext{\$\exitit{\$\text{\$\text{\$\exitit{\$\ext{\$\exitit{\$\ext{\$\exitit{\$\ext{\$\exitit{\$\ext{\$\exitit{\$\ext{\$\exitit{\$\ext{\$\exitit{\$\ext{\$\exitit{\$\ext{\$\exitit{\$\ext{\$\exitit{\$\ext{\$\ext{\$\ext{\$\ext{\$\exitit{\$\ext{\$\ext{\$\exitit{\$\ext{\$\exitit{\$\ext{\$\exitit{\$\ext{\$\exitit{\$\ext{\$\exitit{\$\ext{\$\exitit{\$\ext{\$\exitit{\$\ext{\$\ext{\$\exitit{\$\ext{\$\ext{\$\exitit{\$\ext{\$\exitit{\$\ext{\$\exitit{\$\ext{\$\exitit{\$\ext{\$\exitit{\$\ext{\$\exitit{\$\exitit{\$\ext{\$\exitit{\$\ext{\$\exititit{\$\exitit{\$\exitit{\$\exitit{\$\exitit{\$\exitit{\$\ex 100 105 Gly Pro Cys Arg Ala Ser Phe Pro Arg Trp Tyr Phe Asp Val Glu Arg 115 120 Asn Ser Cys Asn Asn Phe Ile Tyr Gly Gly Cys Arg Gly Asn Lys Asn

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130
                        135
                                            140
Ser Tyr Arg Ser Glu Gl\psi Ala Cys Met Leu Arg Cys Phe Arg Gln Gln
                    150
                                        155
Glu Asn Pro Pro Leu Pro Leu Gly Ser Lys Val Val Leu Ala Gly
                165
                                    170
                                                         175
Leu Phe Val Met Val Leu Ile Leu Phe Leu Gly Ala Ser Met Val Tyr
            180
Leu Ile Arg Val Ala Arg Arg Asn Gln Glu Arg Ala Leu Arg Thr Val
Trp Ser Ser Gly Asp Asp Lys Glu Gln Leu Val Lys Asn Thr Tyr Val
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                                            220
Leu
225
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*A*2

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Xaa Thr Xaa
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Arg Arg Gln Asp Ser Glu Asp His Ser Ser Asp Met Phe Asn Tyr Glu
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                                25
Glu Tyr Cys Thr Ala Asn Ala Val Thr Gly Pro Cys Arg Ala Ser Phe
        35
                            40
                                                45
Pro Arg Trp Tyr Phe Asp Val Glu Arg Asn Ser Cys Asn Asn Phe Ile
Tyr Gly Gly Cys Arg Gly Asn Lys Asn Ser Tyr Arg Ser Glu Glu Ala
                                        75
Cys Met Leu Arg Cys Phe Arg Gln Gln Glu Asn Pro Pro Leu Pro Leu
                85
                                    90
                                                        95
Gly Ser Lys Val Val Leu Ala Gly Ala Val Ser
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Ser Phe Ser Trp
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Glu Glu Pro Gly Ala Cys Pro Ala Xaa Arg Leu Glu Leu Arg Arg
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ccacgggtga cctggccacc agpaggaatg cagcggattc ctctgtccca agtgctccca
                                                                      120
gaaggcagga ttctgaagac cadtccagcg atatgttcaa ctatgaagaa tactgcaccg
                                                                      180
ccaacgcagt cactgggcct tgctgtacat ccttcccacg ctggtacttt gacgtggaga
                                                                      240
ggaactcctg caataacttc atc4atggag gctgccgggg caataagaac agctaccgct
                                                                      300
ctgaggaggc ctgcatgctc cgctbcttcc gccagcagga gaatcctccc ctgccccttg
                                                                      360
gctcaaaggt ggtggttctg gccg\partiaggctg tttcgtgatg gtgttgatcc ttttcctggg
                                                                      420
gagentecat ggtettaetg atte¢gggtg geaaggagga accaggageg tgeeetgegg
                                                                      480
ancgtctgga gcttcggaga tgacdagggn t
                                                                      511
<210>
      76
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      31
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Artificial Sequence
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Ser Phe Ser Trp Gly Ala Ser Met Val Leu Leu Ile Pro Gly Gly Lys
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                                                         15
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Glu Glu Pro Gly Ala Cys Pro Ala Xaa Arg Leu Glu Leu Arg Arg
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gcgacctccg cgcgttggga ggtgtagcgc ggctctgaac gcgtngagng gccgttgagt 6	0
gtcgcaggcg gcgagggcgc gagtgaggag cagacccagg catcgcgcgc cgagaagncg 12	0
ggcgtcccca cactgaaggt cdggaaaggc gacttccggg ggctttggca cctggcggac 18	0
cctcccggag cgtcggcacc tgaacgcgag gcgctccatt gcgcgtgcgt ntgaggggct 24	0
tecegeacet gategegaga eeceaacgge tggtggegte geetgegegt eteggetgag 30	0
ctggncatgt cg 31	2
<pre>&lt;210&gt; 78 &lt;211&gt; 330 &lt;212&gt; DNA &lt;213&gt; Homo sapiens  &lt;220&gt; &lt;221&gt; misc_feature &lt;222&gt; (117)(117) &lt;223&gt; "n" is any nucleotide.  &lt;220&gt; &lt;221&gt; misc_feature &lt;222&gt; (123)(123) &lt;223&gt; "n" is any nucleotide.</pre> <pre>&lt;220&gt; &lt;221&gt; misc_feature &lt;222&gt; (123)(123) &lt;223&gt; "n" is any nucleotide.</pre>	
<400> 78 gcgacctccg cgcgttggga ggtgtagcgc ggctctgaac gcgtgcaggg ccgttgagtg 6	0
tcgcaggcgg cgagggcgcg agtgaggagc agacccaggc atcgcgcgcc gagaagncgg 12	0
gcntccccac actgaaggtc cggaaaggcg acttccgggg gctttggcac ctggcggacc 18	0
ctcccggagc gtggcacctg aacgcgaggc gctccattgc gcgtgcgttt gaggggcttc 24	0
ccgcacctga tcgcgagacc ccaacggctg gtggcgtcgc ctgcgcgtct cggctgagct 30	0
ggccatggcg cactgtgcgg ngctgaggcg 33	0
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ttgagtgtng naggeggega gggeggagt gaggageaga eccaggeate gegegeegag
                                                                      60
aaggccgggc gtccccacac tgaggtccg gaaaggcgac ttccgggggc tttggcacct
                                                                     120
ggcggaccet ceeggagegt egdeacetga aegegaggeg etecattgeg egtgegtttg
                                                                     180
aggggettee egeacetgat egegagaeee caaeggetgg tngegteget negegteteg
                                                                     240
gctgagcttg gccatggcgc antgttncgg gctnaggcgg acg
                                                                     283
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                                                                        60
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cgcaggcggc agggcngadt gaggagcaga cccaggcatc gcgcgccgag aagncgggcg
                                                                      120
tececacact gaaggteedg aaaggegaet teeggggget ttggeacetg geggaegtee
                                                                      180
cggagcnggc acctgaacg¢ gaggcgctcc attgcgcgtg cgtttgaggg gcttcccgca
                                                                      240
cctgatcgcg agaccccaad ggctggtngc gtcgctggcg cgttctcggc tgagctggcc
                                                                      300
atggcgcant gttgcgngct gaggcggacc gncgtttttc ttcgccttgc tgggattcgc
                                                                      360
ttgcttcctn tctgggggtt cctgggcggc cgaccgagaa cgcagcatcc aagaattttt
                                                                      420
                                                                      423
gcc
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gaaaggcgac ttccgggggc tttbgcacct ggcggaccct cccggagcgt cggcacctga
                                                                     120
acgcgaggcg ctccattgcg cgtdcgtntg gaggggcttc ccgcacctga tcgcgagacc
                                                                     180
ccaacggctg gtgggcgtcg ctgcgcgtct tcggctgagc tgggccatgg cgcanttgtt
                                                                     240
gegggetgag geggaegegg negtttttte gneettgetg ggattegttg tinetetetn
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ggggttctgg ggnggccgan cgagaacgca agcattcacg attt
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gcttcccgca cctgatcgcg &gaccccaac ggctggtggc gtcgctgcgc gtctcggctg
                                                                      120
agctggccat ggcgcantgt dgcgngctga ggcggcggnc gttttctcgc ctgctgggat
                                                                      180
egetgeteet etetggggte etggeggeeg accgagaaeg cagcatecae ganttettee
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tggtgttcga agg
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cctccattgc cgtgcgttng aggggcttcc cggaacttga tcgcgagacc ccaacggctg
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gtggcgtcgc tgcgcgtcct cggctgdgct ggccatggcg cantggtgcc gngctgaggc
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cggagggccg gtttctcgcc ttgctgggat cgctgctcct ctctgggggtc ctggcggccg
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ancgaagaan gcagcaatcc angaatthct gcctggtgtt cgaaagttgg tgggcanatt
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ccggggcctt catgnctaag gttggttbgt anaatgtnaa ttaangattc ttgcaactgt
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ttgtgtnatt ggggctntta aacggaahna caataatnac ctgaccaaag aagnaat
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cctccatgcc taggtggtgb tacaatgtca ctgacggatc ctgccagctg tttgtgtatg
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ggggctgtga cggaaacag aataattacc tgaccaagga ggagtgcctc aagaaatgtg
                                                                      240
                                                                      300
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ctgtgacgga aacagcaata attacctgac caaggaggag tgcctcaaga aatgtgccac	240
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cccaagtgct cccagaaggc aggattctga agaccactcc agcgatatgt tcaactatga	360
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                                                                       120
ctctgtccca agtgctccca gadggcagga ttctgaagac cactccagcg atatgttcaa
                                                                       180
ctatgaagaa tactgcaccg ccaacgagt ncactgggcc ttgcgtggca tnccttccca
                                                                       240
cgctngtact ttgacgtgga gagdaactcc tggcaataac ttcatctatg gaggcttgcc
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                                                                      120
aaggcaggat tetgaagace actecagega tatgtteaac tatgaagaat actgeacege
                                                                      180
caacgcagtc actgggcctt gccgtdcatc cttcccacgc tggtactttg acgtggagag
                                                                      240
gaactcctgc aataacttca tctatqgagg ctgccggggc aataagaaca gctaccgctc
                                                                      300
tgaggaggcc tgcatgctcc gctgc‡tccg ccagcaggag aatcctcccc tgccccttgg
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ctcaaaggtg gtggttctgg ccggggctgt ttcgtgatgg tgttgatcct tttcctgggg
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pulsely

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tcctggggag cctccatggt ctacctgatc cgggtggcac ggagggaacc agggagcgtg
                                                                      180
ccctgcgcac cgtctgggag ctccggagat gacaagggag cagctgggtg aagaacacat
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                                                                      120
teegggtgge aeggaggaae eeaggahegt geeetgegea eegtetggag eteeggagat
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gacaaggagc agctggtgaa gaacacatat gtcctgtgac cgccctgtcg ccaagaggac
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gagaatecte ceetgeeest tgdeteaaag gtggtggtte tggegggget gttegtgatg
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gtgttgatcc tcttcctggg ag¢ctccatg gtntacctga tccgggtngc acggaggaac
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cagggagcgt gccctgcgna ccdtctngga gctccggaga tgacaaggag cagctggtga
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agaacacata tgtcctgtga ccdncctgtt cgncaagagg actnggggaa aggggagggg
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tggcggggct gttcgtgatg gtghttgatcc tcttcctggg agcctccatg gtctacctga
                                                                       180
teegggtgge aeggaggaae eag\u00e9gagegt geeetgegea eegtetggga geteeggaga
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agggantggg ggaaggggag ggggaganta ttgttgttga gnttttttt aaaattagga
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•			(					
gtttct	tttg	tttgtctgat	ttatggt	tttt	tttaagtata	aacaaaagtt	ttttattagc	240
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cncatcacag aagtgatgtt ggaatcgttt cttttgtttg tctgatttat ggttttttta
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                                                                  120
attocattgc ctcttttctc atcacagaag tgatgttgga atcgtttctt ttgtttgtct
                                                                  180
gatttatggt ttttttaagt ataaacaaaa gttttttatt agcattctga aagaaggaaa
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